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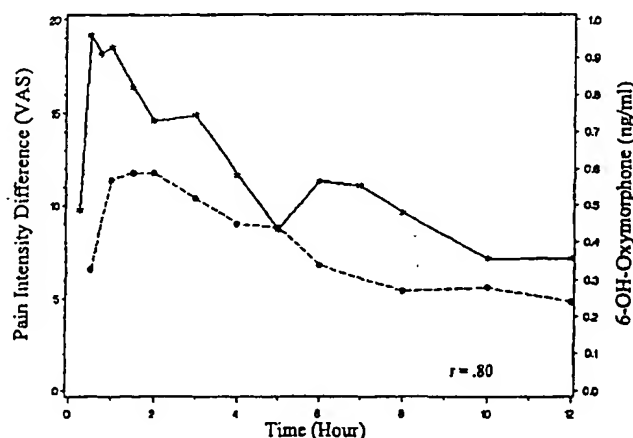
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[Continued on next page]

(54) Title: ORAL ADMINISTRATION OF 6-HYDROXY-OXYMORPHONE FOR USE AS AN ANALGESIC

PK Profile for 6-OH-Oxymorphone with PID Scores



* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

(57) Abstract: In a method of treating pain, a patient is administered a pharmaceutical composition of 6-hydroxy oxymorphone in an amount sufficient to induce analgesia. In one embodiment, the pharmaceutical composition is administered orally. Any known or later developed method of oral delivery may be used. To achieve the desired analgesic effect, blood plasma levels of 6-hydroxy oxymorphone are raised to at least approximately 0.2 ng/mL. Most preferably blood plasma levels of 6-hydroxy oxymorphone range at least 0.3 ng/mL during treatment. Administration of compositions containing 6-hydroxy oxymorphone, and one or more carriers, diluents, and excipients in an amount sufficient to induce analgesia is also contemplated.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**ORAL ADMINISTRATION OF
6-HYDROXY-OXYMORPHONE FOR USE AS AN ANALGESIC**

This application relates to provisional patent application serial nos. 60/329,445 filed October 15, 2001, 60/329,432 filed October 15, 2001, 60/303,357 filed July 6, 2001, and 60/329,444 filed October 15, 2001.

Background

Field of Invention

The invention relates to methods for alleviating pain. More particularly, the invention relates to methods for alleviating pain by administering 6-hydroxy oxymorphone. Most particularly, the invention relates to methods of inducing analgesia by increasing blood plasma levels of 6-hydroxy oxymorphone through oral administration of a pharmaceutical composition containing 6-hydroxy oxymorphone.

Summary of the Invention

The present invention provides methods of treating pain by administering a pharmaceutical composition comprising 6-hydroxy oxymorphone in an amount sufficient to induce analgesia. In one embodiment, the pharmaceutical composition is administered orally. Any known or later developed method of oral delivery may be used. To achieve the desired analgesic effect, blood plasma levels of 6-hydroxy oxymorphone are raised to at least about 0.2 ng/mL. Most preferably blood plasma levels of 6-hydroxy oxymorphone of at least about 0.3 ng/mL during treatment. Methods for administering compositions comprising 6-hydroxy oxymorphone, and one or more carriers, diluents, and excipients in an amount sufficient to induce analgesia are also provided.

Brief Description of the Drawings

Fig. 1 is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

Fig. 2 is a pharmacokinetic profile for oxymorphone with PID scores.

Fig. 3 is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain scores.

Fig. 4 is a pharmacokinetic profile for oxymorphone with categorical pain scores.

Detailed Description

The methods described herein provide for the administration of a pharmaceutical composition containing 6-hydroxy oxymorphone as an active ingredient. In a preferred embodiment the preferred composition comprises 6-hydroxy oxymorphone alone (excepting, of course, carriers, diluents, and other excipients). In other preferred embodiments, 6-hydroxy oxymorphone may be combined with other opioids or other pharmaceutical agents. For example, another preferred embodiment provides compositions comprising both 6-hydroxy oxymorphone and its parent, oxymorphone.

In two separate studies, blood plasma levels and indications of pain relief were recorded over a 12 hour period after. Figs. 1-4 show graphical representation of the data combining the two studies such that the effect of blood plasma levels of oxymorphone and its metabolite, 6-hydroxy oxymorphone on pain can be evaluated.

The administration of oxymorphone yields blood plasma levels of oxymorphone and all of its metabolites, 6-hydroxy oxymorphone. Oxymorphone levels peak within 2 hours, fall slightly, and plateau. Interestingly, the level spikes again at 4-6 hours from administration. After this time, oxymorphone levels again drop and eventually fall to levels near the earlier plateau.

Like oxymorphone, 6-hydroxy oxymorphone blood plasma levels peak within 2 hours after administration. After the initial peak, however, a more or less steady decline in the 6-hydroxy oxymorphones plasma levels is observed.

Comparing these levels to the pain profiles, a correlation between the 6-hydroxy oxymorphone blood plasma levels and pain relief can be seen. The pain levels nearly mirror the 6-hydroxy oxymorphone levels, with substantial rises in relief near the spikes associated with 6-hydroxy oxymorphone blood levels. Thus, pain relief can be achieved through administration of 6-hydroxy oxymorphone alone.

In addition to the pharmacokinetic studies, binding studies have been conducted to compare the binding affinity of 6-hydroxy oxymorphone to that of oxymorphone. The results are reported in TABLE 1. These results clearly indicate that 6-hydroxy oxymorphone has great binding affinity for the δ , κ , and μ receptor cites, comparable to the binding affinity of its parent. The inventors believe that by virtue of this binding

affinity, 6-hydroxy oxymorphone has similar analgesic effects to its parent, oxymorphone.

TABLE 1: ASSAY REPORT

	6-HYDROXY OXYMORPHONE		OXYMORPHONE	
	10nm 1.0 E-8	10 μ m 1.0 E-5	10nm 1.0 E-8	10 μ m 1.0 E-5
Opiate, Delta 1	-4.12%	90.48%	-18.26%	89.03%
Opiate, Delta 2 (Human Recombinant)	7.19%	55.45%	7.76%	72.74%
Opiate, Kappa (Human Recombinant)	2.45%	62.47%	10.35%	89.41%
Opiate, Mu (Human Recombinant)	63.16%	99.91%	85.42%	100.39%

Accordingly, methods of administering the metabolite, 6-hydroxy oxymorphone, directly have been developed. It is believed that the β isomer has greater efficacy in the treatment of pain, but this disclosure is not limited to use of that isomer alone. Pharmaceutical compositions containing either 6- α -hydroxy oxymorphone, 6- β -hydroxy oxymorphone, or mixtures thereof can be used in the invention.

Formulation as a suspension, syrup, or other liquid, tablet, capsule, liquid-filled gel cap, or other solid or semi-solid means may be used. The composition may alternately be in the form of a time release formulation, including timed, suspended and extended release formulations. Regardless of the formulation, an amount of 6-hydroxy oxymorphone sufficient to induce analgesia will be supplied to the patient. Blood plasma levels of 6-hydroxy oxymorphone must be raised to levels sufficient to induce the desired level of analgesia.

The amount administered will be dependent upon normal criteria such as patient weight, intensity of pain, and other factors. Based on the pharmacokinetic studies, blood plasma levels around at least 0.2 ng/mL will provide some analgesia. The upper plasma level limit will be ultimately established by safety concerns. Over-dosing of any opioid, including 6-hydroxy oxymorphone, may lead to respiratory failure and other undesirable side effects and can even result in death. Preferably, the blood plasma level of 6-hydroxy oxymorphone will be raised to at least 0.3 ng/mL. Subsequent doses may be required to maintain these blood levels.

The preferred administration is of 6-hydroxy oxymorphone with appropriate carriers and excipients as will be readily apparent to those skilled in the art. The resulting blood plasma in these preferred administrations will therefore be substantially free of oxymorphone.

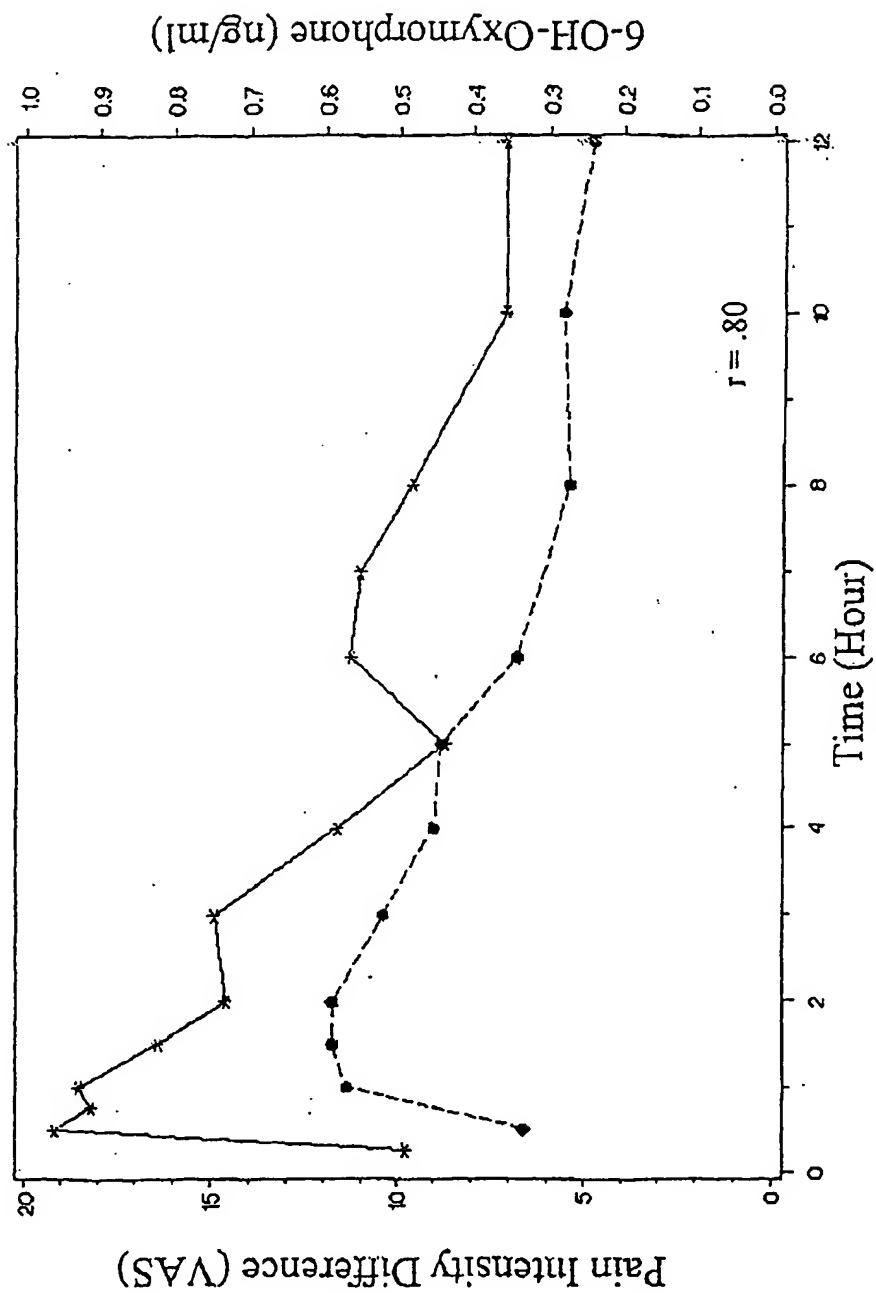
The above description encompasses some preferred embodiments of the invention. This disclosure is merely illustrative in nature and is not intended to limit the following claims.

CLAIMS

What is claimed is:

1. A method of treating pain comprising the step of:
administering to a patient a pharmaceutical composition comprising 6-hydroxy oxymorphone in an amount sufficient to induce analgesia.
2. ~~The method of claim 1 wherein said pharmaceutical composition is administered orally.~~
3. The method of claim 2 wherein said pharmaceutical composition is administered in a form selected from a liquid formulation, syrup, suspension, solid formulation, tablet, capsule, liquid-filled gel cap, and a semi-solid formulation.
4. The method of claim 1 wherein said administration is sufficient to raise blood plasma levels of 6-hydroxy oxymorphone to at least about 0.2 ng/mL.
5. The method of claim 1 wherein said administration is sufficient to raise blood plasma levels of 6-hydroxy oxymorphone to at least about 0.3 ng/mL.
6. A method of treating pain comprising the step of:
orally administering to a patient a pharmaceutical composition comprising 6-hydroxy oxymorphone, and one or more carriers, diluents, and excipients in an amount sufficient to induce analgesia.
7. A method of treating pain comprising the step of:
orally administering to a patient a pharmaceutical composition comprising 6-hydroxy oxymorphone and oxymorphone in an amount sufficient to induce analgesia.
8. A pharmaceutical composition comprising 6-hydroxy oxymorphone in a formulation for oral delivery to animals including humans.

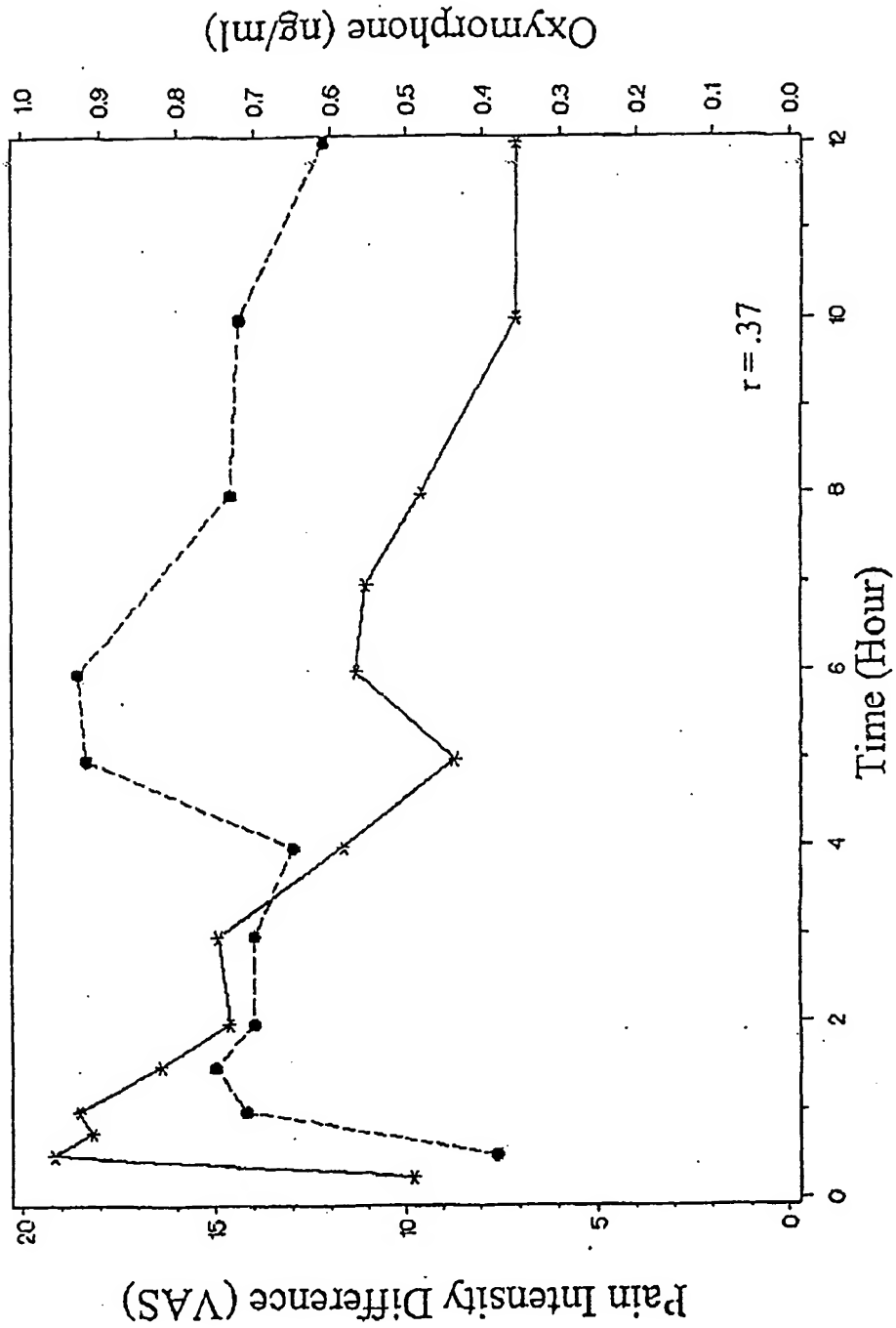
PK Profile for 6-OH-Oxymorphone with PID Scores



* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

FIG. 1

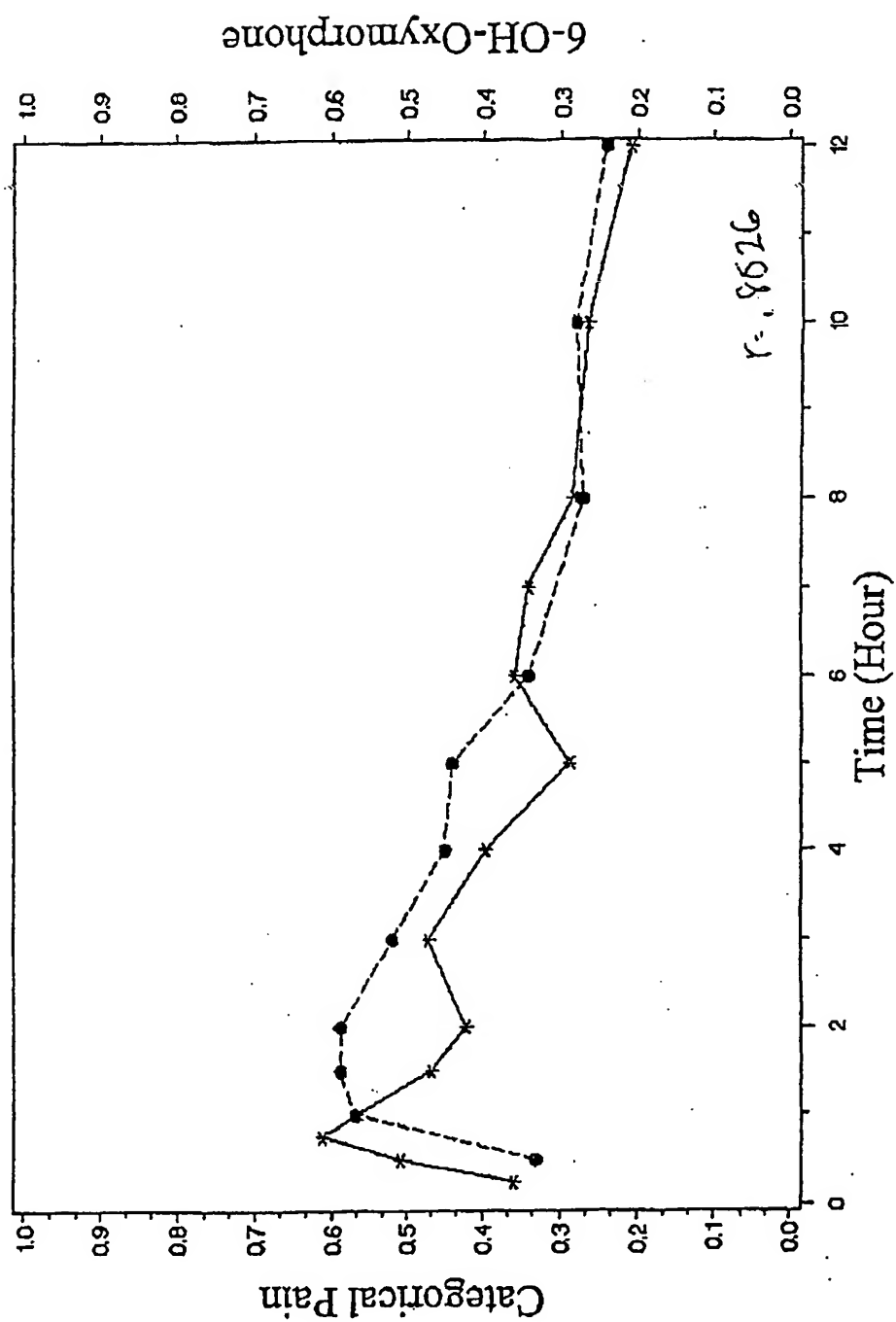
PK Profile for Oxymorphone with PID Scores



* Pain Intensity Difference. • Oxymorphone Plasma Concentrations

FIG. 2

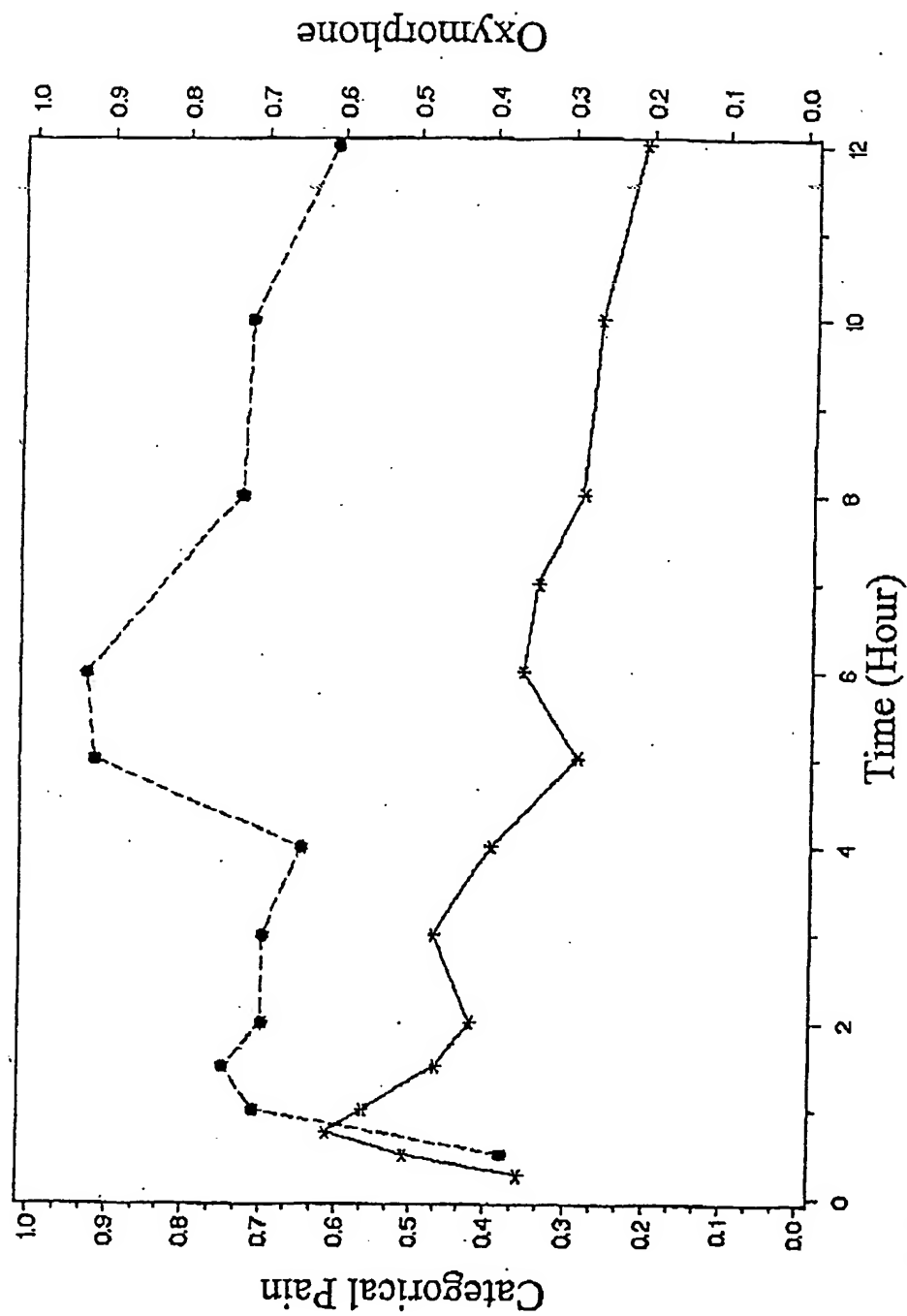
PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores



* Categorical Pain ● 6-OH Oxymorphone Plasma Concentrations

FIG. 3

PK Profile for Oxymorphone with Categorical Pain Scores



* Categorical Pain • Oxymorphone Plasma Concentrations

FIG. 4

INTERNATIONAL SEARCH REPORT

In ional Application No

PCT/US 02/21400

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/485 A61K9/00 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, EMBASE, SCISEARCH, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>CONE, EDWARD J.: "General procedure for the isolation and identification of 6-.alpha.- and 6-.beta.-hydroxy metabolites of narcotic agonists and antagonists with a hydromorphone structure"</p> <p>J. CHROMATOGR. (1976), 129, 355-61 , XP001106444</p> <p>page 356; table 1</p> <p>page 357, paragraph SECOND</p> <p>page 361</p>	1-8
Y	<p>US 6 166 211 A (DRUMMOND JR SPENCER ET AL) 26 December 2000 (2000-12-26) column 2</p> <p>---</p> <p>---</p> <p>---</p>	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Δ document member of the same patent family

Date of the actual completion of the international search

23 October 2002

Date of mailing of the international search report

31/10/2002

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/21400

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CONE E J ET AL: "Oxymorphone metabolism and urinary excretion in human, rat, guinea pig, rabbit, and dog." DRUG METABOLISM AND DISPOSITION, (1983 SEP-OCT) 11 (5) 446-50. , XP001106446 ...abstract page 446, right-hand column ---	1-8
Y	US 4 844 907 A (ELGER GORDON A ET AL) 4 July 1989 (1989-07-04) claims 1,2 ---	1-8
Y	US 5 629 011 A (ILLUM LISBETH) 13 May 1997 (1997-05-13) claims 1,9 ---	1-8
Y	US 4 366 159 A (MAGRUDER MICHAEL R) 28 December 1982 (1982-12-28) column 3, line 35-37 - line 55-59 -----	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/21400

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Original Application No

PCT/US 02/21400

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6166211	A	26-12-2000	AU 3736500 A WO 0056735 A1	09-10-2000 28-09-2000
US 4844907	A	04-07-1989	AT 46437 T AU 584234 B2 AU 6183086 A CA 1272955 A1 DE 3665669 D1 DK 407286 A EP 0220805 A2 IE 59515 B JP 1948471 C JP 6081733 B JP 62051625 A NZ 217341 A SG 94892 G ZA 8606207 A	15-10-1989 18-05-1989 05-03-1987 21-08-1990 26-10-1989 01-03-1987 06-05-1987 09-03-1994 10-07-1995 19-10-1994 06-03-1987 28-10-1988 04-12-1992 29-04-1987
US 5629011	A	13-05-1997	AT 171872 T AU 3458093 A CA 2127805 A1 DE 69321458 D1 DE 69321458 T2 DK 625044 T3 EP 0625044 A1 ES 2123660 T3 WO 9315737 A1 GB 2277682 A , B JP 7503481 T NO 942787 A	15-10-1998 03-09-1993 19-08-1993 12-11-1998 18-03-1999 21-06-1999 23-11-1994 16-01-1999 19-08-1993 09-11-1994 13-04-1995 27-07-1994
US 4366159	A	28-12-1982	AR 228984 A1 AU 549070 B2 AU 8804282 A CA 1200501 A1 EP 0074105 A1 FI 823112 A GR 76702 A1 HU 190699 B IL 66743 A JP 58055422 A NZ 201841 A PH 18772 A PT 75521 A ZA 8206500 A	13-05-1983 09-01-1986 17-03-1983 11-02-1986 16-03-1983 09-03-1983 29-08-1984 28-10-1986 31-07-1986 01-04-1983 14-12-1984 25-09-1985 01-10-1982 25-04-1984